Drivers of Rift Valley fever epidemics in Madagascar

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Rift Valley fever (RVF) is a vector-borne viral disease widespread in Africa. The primary cycle involves mosquitoes and wild and domestic ruminant hosts. Humans are usually contaminated after contact with infected ruminants. As many environmental, agricultural, epidemiological, and anthropogenic factors are implicated in RVF spread, the multidisciplinary One Health approach was needed to identify the drivers of RVF epidemics in Madagascar. We examined the environmental patterns associated with these epidemics, comparing human and ruminant serological data with environmental and cattle-trade data. In contrast to East Africa, environmental drivers did not trigger the epidemics: They only modulated local Rift Valley fever virus (RVFV) transmission in ruminants. Instead, RVFV was introduced through ruminant trade and subsequent movement of cattle between trade hubs caused its long-distance spread within the country. Contact with cattle brought in from infected districts was associated with higher infection risk in slaughterhouse workers. The finding that anthropogenic rather than environmental factors are the main drivers of RVF infection in humans can be used to design better prevention and early detection in the case of RVF resurgence in the region.

vector-borne infection | zoonosis | El Niño | cattle trade | One Health

Rift Valley fever (RVF) is a vector-borne infection caused by the RVF virus (RVFV). Mosquito species from the *Aedes*, *Culex*, and *Mansonia* genera are the main RVFV vectors (1). The virus persists in the environment either by vertical transmission occurring in some *Aedes* species or by an enzootic cycle involving ruminants and mosquitoes. When environmental conditions are favorable to mosquito proliferation, this cycle is amplified by *Culex* populations, leading to RVF epidemics (2). In the Horn of Africa, these circumstances are met during the warm phases of El Niño southern oscillation (ENSO) and the Indian Ocean dipole zonal mode: Warm sea-surface temperatures in the equatorial eastern-central Pacific Ocean and the western equatorial Indian Ocean result in heavy autumn rainfall and subsequent greening of the vegetation (3–5). The latter can be monitored by the remotely sensed normalized difference vegetation index (NDVI). Besides these environmental conditions triggering epidemics, long-distance RVFV dissemination is often related to ruminant trade (6), as reported in Madagascar and Saudi Arabia (7–9).

In domestic ruminants, the RVFV causes mass abortions and high neonatal mortality (10). Humans may get infected after the bites of infected mosquitoes or the consumption of raw milk. However, most clinical cases occur after contact with blood, aborted fetuses, and placenta of viremic animals. Farmers, veterinarians, slaughterhouse workers, and butchers are thus the most exposed to the risk of RVF, as well as any people attending the slaughtering of viremic animals (11): Blood aerosol produced on this occasion is highly infectious (12). The virus is not transmitted from person to person.

In Madagascar, the first known RVF epidemic occurred in 1990–1991 on the East Coast and in the central highlands (7). A second epidemic occurred in 2008–2009 with official reports suggesting at least 700 suspected cases and 26 RVFV laboratory-confirmed fatalities. However, due to underreporting, an excess of 10,000 human cases was estimated (13–15).

Madagascar is one of the poorest countries in the World, with 90% of the population living with less than USD 1.5 inhab.$^{-1}$·d^{-1} (16). Because public health resources are limited in such a setting, it is crucial to identify the most exposed populations, based on scientific evidence. To this end, we aimed at understanding the circumstances in which RVF epidemics occurred. We first assessed the risk of RVFV introduction to ruminants via livestock trade. Then, we described the environmental conditions associated with the start of the 1990 and 2008 epidemics and with local RVFV transmission. We then aimed to build risk indexes of RVFV human infection related to the local environment (local risk) and cattle trade (remote risk), assess their relative

Significance

Rift Valley fever (RVF) is an emerging, mosquito-borne viral infection of ruminants, transmissible to people, and linked to rainfall. By investigating a wider range of possible drivers this study confirms the assumption that RVF occurrence can also be dependent on nonenvironmental drivers. In Madagascar, human and ruminant infections were geographically distinct, with introduction and long-distance disease spread linked to livestock trading. Human infections were highest in those involved with slaughtering and handling fresh meat. The identification of possible introduction routes, major cattle trade hubs, and areas of high risk to ruminants has shown how multidisciplinary analyses are needed to properly understand disease dynamics and spread, thereby improving early detection and prevention of RVF in humans.

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importance, identify and map high-risk areas, and assess the consequences for human health.

Results

Risk of Virus Introduction by Livestock Trade. Queries in the United Nations (UN) ComTrade database did not reveal direct importations of live ruminants from mainland Africa to Madagascar. However, they highlighted several official importations from the Union of Comoros in 2005–2007 (Table 1). Although the numbers are small, they confirmed the risk of RVFV introduction in Madagascar from an infected country, via livestock trade.

In addition to this official trade, illegal cattle movements between the Comoros Archipelago and Madagascar were probably much more frequent. Informal surveys conducted in 2009 and 2010 in the main Comoros harbors and in the northwest of Madagascar (Mahajanga and Antsiranana) revealed the frequent presence of cattle and small ruminants on board freighters and *botry* (dhows) traveling from the Comoros Islands to Madagascar and from port to port. This coastal navigation is widespread in Madagascar, given the weakness of the terrestrial-road network (Fig. S1). Therefore, RVFV could have been introduced to Madagascar through ruminant trade from Comoros Islands—which were previously infected (17, 18)—and further disseminated through coastal navigation between Malagasy sea ports.

Environmental Conditions and RVFV Epidemics.

Triggering RVF epidemics. Conditions at the start of the two RVF epidemics in humans (March 1990 and January 2008) are shown on Fig. 1. For the three indicators [southern oscillation index (SOI), rainfall, and NDVI] and three biomes (Fig. S2*A*), the two epidemics did not occur in typical RVF conditions according to the eastern African standards (14). In March 1990, a marked negative anomaly was observed for SOI, one of the main indicators of ENSO (Fig. 1*A*). Rainfall was lower than normal in all three biomes (Fig. 1*B*). March 1990 was also at the end of a period of positive NDVI anomalies and before a short period of negative anomalies for the dry forest and xeric shrubland. The NDVI pattern was not clear for the moist forest where the epidemics started (Fig. 1*C*). Conditions during the 2008 epidemic were almost the reverse as it occurred during a cold (positive) anomaly of SOI, when rainfall was close to normal in the moist forest and somewhat higher than normal in the two other biomes.

These general impressions were corroborated by the results of partial triadic analysis and hierarchical clustering (Fig. S3): The environmental conditions of RVF epidemics fell into quite different clusters in 1990–1991 and in 2008–2009: With a three-class partition, the 1990 epidemics occurred in a category of rainy seasons with close-to-normal mean values for SOI (0.01), rainfall (0.16), and NDVI (−0.11). In 2008, the epidemic fell into a category with a high mean SOI (1.38) and close-to-normal mean values for NDVI (0.07) and rainfall (−0.16).

RVFV spread at the end of 2008 epidemic. We modeled the sero-prevalence rate of immunoglobulins of type G (IgG) in ruminant sera collected at the end of the 2008 epidemic to assess the role of environmental conditions in RVF spread in livestock. The subset of plausible models according to the available data is shown in Table S1. The importance of environmental predictors with respect to the selected subset of plausible models is displayed in Table S2. Multimodel averaged coefficients are shown in Table S3. Higher rainfall, municipalities within 50 km from a sea port, and lower altitude were associated with higher sero-prevalence rate in ruminants. See *SI Results* and Figs. S4 and S5 for details on exploratory data analysis.

The receiver operating characteristic (ROC) curve for the averaged model had an area under the curve of 74%. The map of predicted sero-prevalence rate showed high-risk areas on the northwestern and northeastern coasts (lowlands). Southern regions and highlands were less affected with the exception of sea-port municipalities (Fig. 2). See *SI Results* for details.

The Cattle Trade Network and RVFV Dissemination. Cattle trade data were collected monthly from 2007 to 2011, with large variations in numbers across the years. The overall network activity is presented in Fig. S6*A*: Each segment corresponds to a link between two nodes; a segment is drawn if at least one movement has been recorded along that link on a given month; its color is related to its recorded frequency during the 5-y survey. To assess the influence of the cattle trade network on the risk of RVFV in humans, we quantified the trade flows using the most

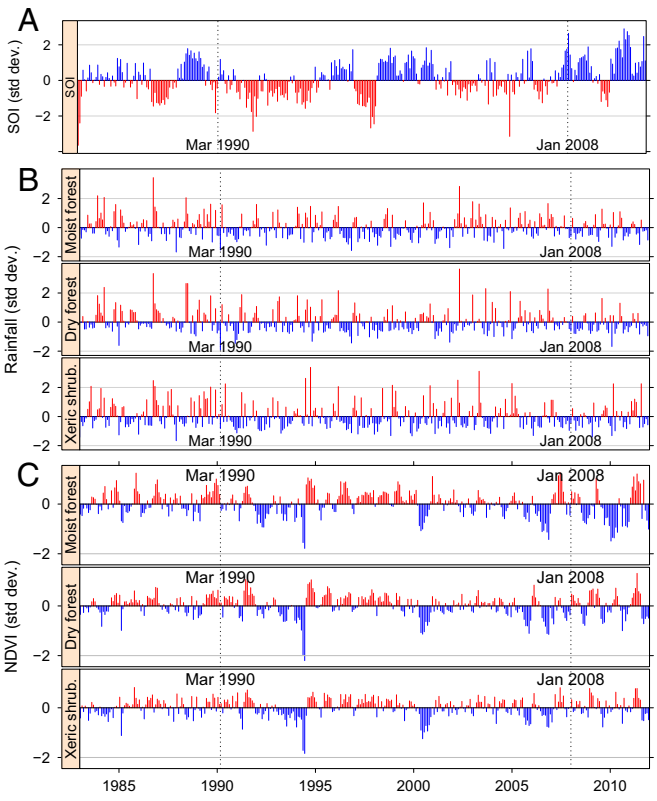

Fig. 1. Environmental conditions (monthly average) in the main Malagasy biomes with respect to the 1990–1991 and 2008–2009 RVF epidemics. (*A*) Standardized southern oscillation index (19). (*B*) Standardized rainfall anomalies. Source: National Oceanic and Atmospheric Administration (NOAA)'s precipitation reconstruction over Land (PREC/L) provided by the NOAA/Office of Oceanic and Atmospheric Research/Earth Sciences Research Laboratory - Physical Sciences Divisions, Boulder, CO. (*C*) Standardized NDVI anomalies. Source: Global Inventory Modeling and Mapping Studies (GIMMS), Advanced Very High Resolution Radiometer (AVHRR) NDVI version 3 (20). On each plot, favorable conditions for RVF are shown in red.

Table 1. Importation of live ruminants in Madagascar from the Union of Comoros between 2005 and 2007 (source: UN ComTrade)

Year	Species	Quantity, head
2005	Cattle	30*
	Goats	9*
2006	Goats	14*
2007	Cattle	7
	Goats	88
	Sheep	47

*Estimated number from the reported financial value. No imports of live ruminants were reported from the Union of Comoros in 2003 and 2004.

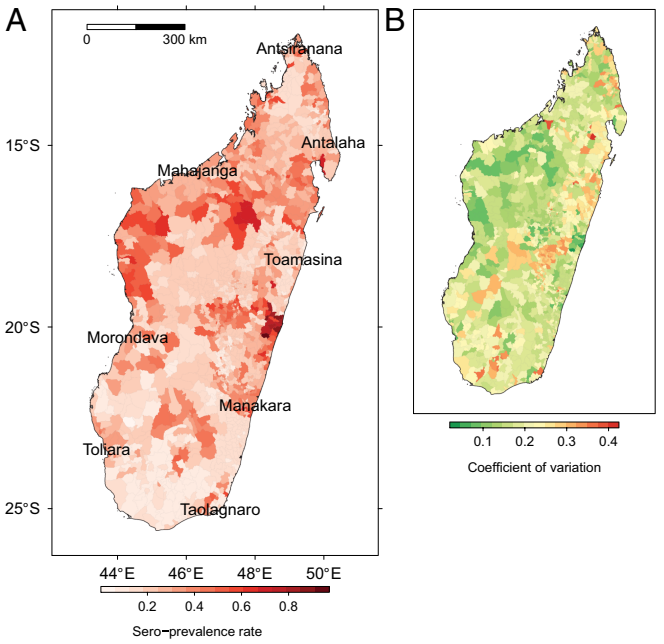

Fig. 2. Sero-prevalence rate of anti-RVFV IgG in ruminants (Madagascar) predicted by the averaged beta-binomial logistic regression model: (*A*) predicted rate and (*B*) coefficient of variation.

comprehensive dataset, collected in 2010. This network had the largest number of nodes (257 farms, markets, and slaughterhouses) and links (346). We could distinguish two sets of links: those active throughout the year (56% of the links) constituting the backbone of the network and those occasional links active for 1 mo or 2 mo. Despite their large number, only a small volume (3%) of animals was traded on these occasional links. Most of the backbone nodes and links active in 2010 were already present in the previous year.

To assess the role of the occasional links on RVFV spread, we considered separate monthly network snapshots and we evaluated the corresponding epidemic threshold q (21), which provides an estimate of the critical probability for the virus to spread through the network: The lower its value is, the higher the risk of spread. The backbone network was the smallest in January (rainy season) and then increased until reaching its plateau size in April (early dry season) (Fig. S6*B*). The number of occasional links peaked in May and October. Despite these large variations, q was slightly affected by the presence of these occasional links. Conversely, it was strongly influenced by the variations of trade volume in the backbone network. The whole network was prone to the diffusion of RVFV: The average epidemic threshold was $\bar{\hat{q}} \simeq 2.1\%$, the period of maximum risk from March to May, with $\hat{q} \simeq 1.5\%$, and the minimum risk ($\hat{q} \simeq 3.9\%$) in January.

The distribution of in/out degrees (number of incoming/outgoing links for a given node) matched a power-law distribution. Only a few nodes (Ihosy, Tsiroanomandy, Ambalavao, and Mampikony) were highly connected hubs and also had the highest betweenness. The four network hubs belonged to three different giant strong components (GSC)—Ambalavao and Ihosy were in the same one. Nodes belonging to these GSC were strongly connected between themselves, thus increasing the risk of infection for other locations in their neighborhood (22). These hubs were also cut points in the network: Their removal would disrupt the network connectedness and thus limit the diffusion of an infectious agent like RVFV.

The pastoral areas of southwest and northwest of Madagascar were the major sources of the traded cattle (Fig. 3*A*) and were characterized by high cattle density and low human density. The great majority of markets had a negative balance in cattle flows: They were sources in the network, with low local consumption (Fig. 3*B*). On the other hand, two hubs (Ambalavao and Tsiroanomandy) had a large, positive balance. Further information is provided on Fig. 3*C*: Cattle were collected in the markets of Tsiroanomandy and Ihosy and then sent to Ambalavao for slaughtering, Tsiroanomandy also being a consumption center. In addition, a close examination of these four hubs showed that many small, outgoing flows offered numerous opportunities for long-distance RVFV spread.

Cattle Trade and the Risk of RVFV Infection in Humans. The coefficient for the local, environment-related index of RVFV transmission to humans was not significant, in contrast to the coefficient for the remote, cattle trade-related index (Table S4 and Fig. S7). The odds ratio (OR) for the latter was $OR_C = 1.7$ (95% confidence interval (CI): [1.1; 2.7]). The risk of humans getting infected with RVFV increased with the intensity of cattle trade from areas with infected livestock.

The map of predicted sero-prevalence rate in humans (Fig. 4) and the plot of random variations (Fig. S8) both highlighted large spatial variations in the infection rate, with a clear spatial pattern. The highest sero-prevalence rates were encountered in the densely populated areas of central highlands. This pattern is emphasized in Fig. S8*B*: A strong additional risk (with respect to cattle trade-related risk) was found in the regions of Antsirabe and Lake Alaotra. See *SI Results* for details.

Discussion

Cattle Trade and the Risk of RVFV Introduction. Imports of live ruminants from Comoros were the main driver for RVFV introduction to Madagascar livestock and subsequent trade-related movements of cattle led to its spread to humans, at least in 2008. Phylogenetic studies showing that Malagasy RVFV were closely related to viruses previously circulating in mainland Africa (15) suggest that RVFV was probably introduced into the Comoros Islands through cattle trade with East Africa (23). The existence of illegal livestock importation from the Comoros Islands provided opportunities for the introduction of RVFV in Madagascar. Preventing such introductions is therefore essential to avoid further RVF epidemics in Madagascar. In practice, strengthening communication between African, Comoros, and Malagasy public health and veterinary services would be important to share early detection in the event of new RVFV circulation. Also, quarantine measures should be reinforced for ruminants exported from continental Africa to the Comoros Islands.

Environmental Conditions and RVF Epidemics. Anyamba et al. (14) has already pointed out the contrasting behavior of the disease in Madagascar and East and South Africa. Prolonged heavy rainfall and positive NDVI anomalies occurred after the first known epidemics of 1990, e.g., in 1994 with the occurrence of the Geralda cyclone (24). More recently, torrential rainfall occurred in February–March 2015 in Madagascar, related to the strong El Niño conditions (25). No RVF outbreak could be detected despite specific surveillance measures in 1994 (shortly after the 1990–1991 RVF epidemic) and strengthened national and regional surveillance in 2015 (26, 27).

RVF epidemics usually start in the arid environments of *dambos* (East Africa) and/or *pans* (southern Africa) (1), which are similar to ecosystems in the Toliara region of southwest Madagascar that are covered by xeric shrublands (Fig. S2*A*). Although this sea-port municipality was hit by RVF, the sero-prevalence rate in ruminants was low in the neighboring municipalities (Fig. 2), probably because the virus was introduced in suboptimal conditions for the vectors (no heavy rainfall, no flooding). Conversely, high sero-prevalence rates were observed in cattle in the northwest of the island, covered by the dry forest. Moreover,

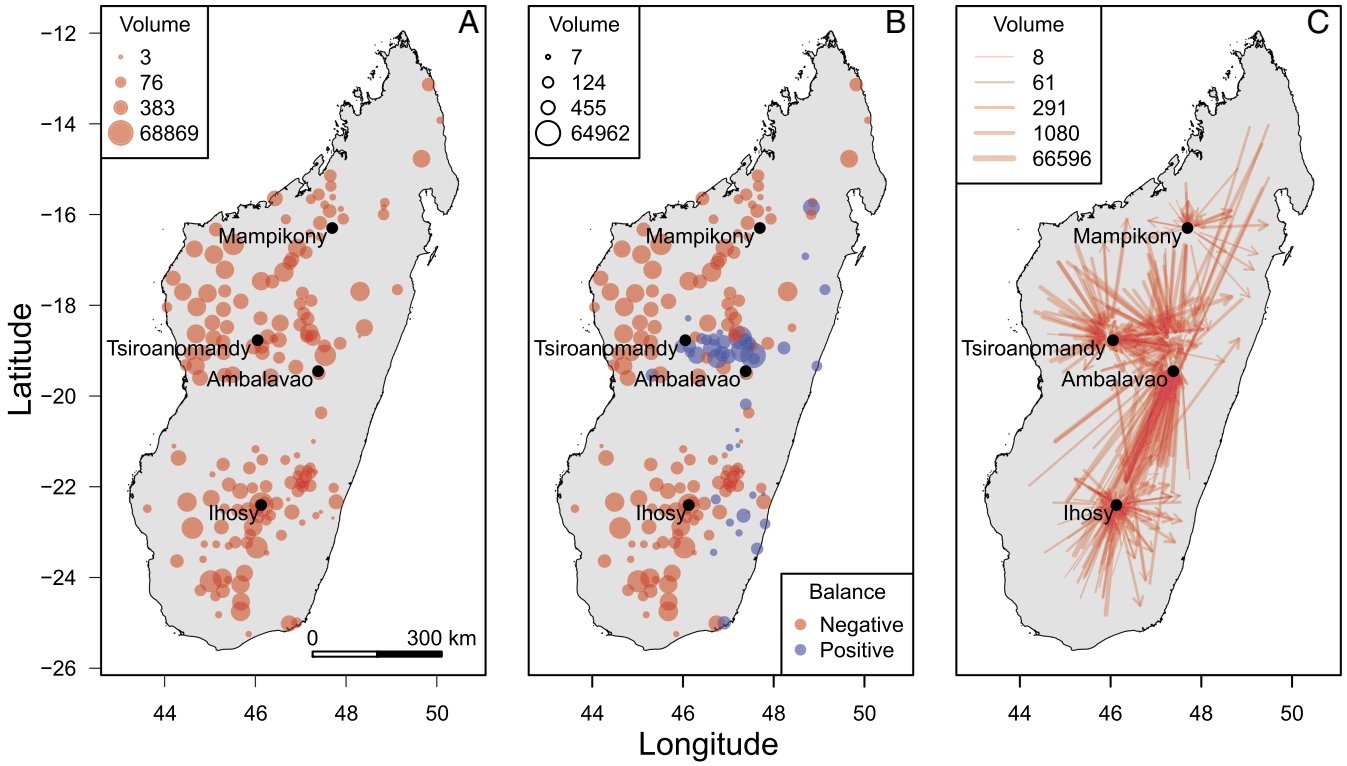

Fig. 3. Cattle flows in the Malagasy cattle trade network, 2010. (*A*) Municipality of origin (number of flows). (*B*) Balance in cattle flows at the municipality level (number of heads). (*C*) Directed flows (number of heads).

in East Africa, *Aedes* mosquitoes are the primary RVFV vectors (1): Their biology and ecology are well adapted to arid environments. Regarding Madagascar, 23 mosquito species might be considered as potential RVFV vectors, including no floodwater *Aedes* mosquito species (28–30). A single species, *Culex antennatus*, meets all criteria for formal classification as an RVFV vector (31). This mosquito is widespread in Madagascar (except in the North), including in rice paddies that cover large areas of the island. The introduction of infected animals in conjunction with *Culex* hatching, during a standard rainy season profile, might have amplified the outbreak locally, in many places.

Two major differences are thus highlighted between Madagascar and East Africa: (*i*) the lack of connection between the start of 1990–1991 and 2008–2009 RVF epidemics and El Niño events and, more generally, with anomalous heavy rainfall and (*ii*) no obvious role of *Aedes* mosquitoes in the primary RVFV transmission cycle, as well as the wide distribution of *Culex* (and other mosquito species).

Apparently, the climatic conditions observed during the two epidemics are common in Madagascar: The drivers triggering RVFV epidemics must therefore be sought elsewhere. Nevertheless, these climatic conditions remain important for the amplification of the primary epidemiological cycle between mosquitoes and ruminants (Table S2).

Cattle Trade as a Driver of RVF Epidemics. The Malagasy population is growing fast, from 16 million to 24 million between 2000 and 2015 (16), and is concentrating in Antananarivo and other large cities (Fig. S2*B*). Cattle are omnipresent in Malagasy agriculture, economy, and culture. This leads to an ever-growing demand for cattle meat and draught power for crops. Consequently, the increasing cattle trade provides more opportunities for RVF epidemics to spread (7, 8). Our description of the national cattle trade network strongly supports this assumption and further extends a previous analysis in the North of Madagascar (8). The connectedness of the cattle trade network and its low percolation threshold make the risk of seeding epidemics high.

Lake Alaotra and Antsirabe (Fig. S2*A*) are two major crop and livestock farming regions. The former is the largest rice-production basin in Madagascar, with many paddies and swamps

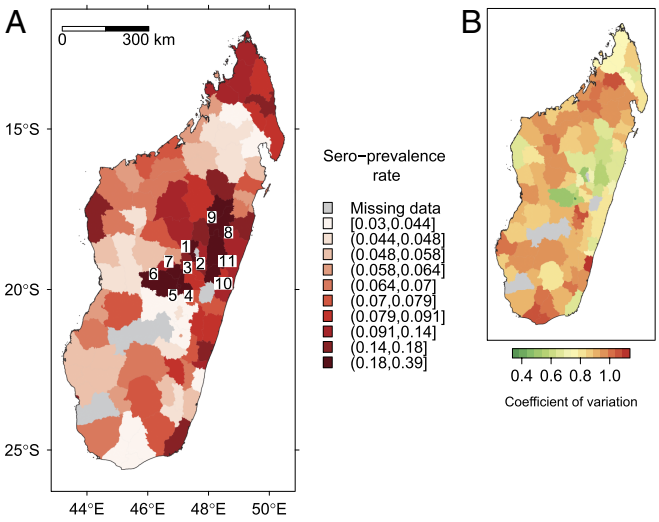

Fig. 4. Sero-prevalence rate in humans predicted by a mixed-effect binomial logistic regression model: (*A*) predicted rate and (*B*) coefficient of variation. In *A*, numbers were placed at the centroid of districts with the highest predicted rates (10th decile): 1, Ambohidratrimo; 2, Antananarivo Renivohitra; 3, Antananarivo-Sud; 4, Antsirabe Rural; 5, Antsirabe Urban; 6, Betafo; 7, Faratsiho; 8, Ambatondrazaka; 9, Amparafaravola; 10, Anosibe; and 11, Moramanga.

favorable to mosquito proliferation. The two regions are densely populated, with cities harboring big livestock markets and slaughterhouses to match local red meat needs. Therefore, there are many opportunities for human exposure to the RVFV when viremic animals are slaughtered.

Additionally, using the network of markets, butcheries, and *hotely* (cheap restaurants for travelers), farmers try to sell their sick animals at the first clinical sign of any disease, to mitigate economic losses. When they do not succeed, they slaughter them and eat their meat (32). This practice was probably at the origin of many unreported human infections during the 2008–2009 RVF epidemics in Madagascar.

More collaboration with sociologists and anthropologists is needed to decipher farmers' perceptions of animal diseases and to assess the social acceptability of prevention, surveillance, and control measures, such as cattle vaccination to protect people (should enough vaccine be available) or cattle movement restrictions to avoid RVFV spread through hubs in the cattle trade network (33). If RVFV introduction into Malagasy livestock continues, targeted (risk-based) vaccination campaigns of ruminants might be organized to protect human populations. Individual protection measures, such as vaccination when the human vaccine becomes available or wearing personal protective equipment such as gowns, gloves, safety glasses, and masks when slaughtering ruminants would also be important to implement in the most exposed categories of people (34, 35), together with dissemination and training programs. This implementation of coordinated actions between Public Health and Veterinary Services would represent an important advance in the so-called "One Health" joint approach of human and animal health (27, 36).

Materials and Methods

To assess the risk of RVFV introduction, we scanned national and international databases on sea trade from 2003 to 2008. We also implemented informal surveys in harbors of the Comoros Islands and northwestern Madagascar during and after this epidemic (up to 2010).

To describe the environmental conditions of the past RVF epidemics, we used global datasets available as long-term time series: (*i*) the SOI as a main indicator of ENSO of major importance for the climatic conditions in East Africa and the southwest tropical Indian Ocean (3); (*ii*) rainfall data, of crucial importance for the epidemiology of vector-borne diseases (37); and (*iii*) the NDVI as an indicator of rainfall impact on the vegetation (38): forage resources for ruminants and resting sites for mosquitoes. These indicators were averaged over the main biomes (*SI Materials and Methods*). First, we plotted the time series for each biome. Second, we selected data from the dry-forest biome where the highest sero-prevalence rate was observed in cattle in 2008 (39). We then used partial triadic analysis (PTA), a multitable version of principal component analysis (PCA) (40), to identify common or contrasted patterns in rainy seasons (November to March) from 1983 to 2011 (28 y).

To assess the risks of RVFV spread within Madagascar, we used two types of data: (*i*) environmental data selected among the factors of interest for mosquito-borne infections, i.e., related to the availability of resting or breeding sites or the seasonal changes in conditions favoring the development of their immature stage, etc. (37) (see the list in *SI Materials and Methods*), which were obtained from international databases and processed using standard methodology; and (*ii*) cattle trade data collected during repeated nationwide surveys in livestock markets and slaughterhouses, implemented from 2007 to 2011 for the purpose of this study.

Environmental data were used in beta-binomial logistic regression (BBLR) models to predict the RVFV sero-prevalence rate for cattle at the municipality level. The serological data were collected after the 2008 epidemics and published (39). Sera were tested for the presence of anti-RVFV IgG. We adopted a multimodel inference approach to select the best predictors. A set of plausible models was kept for model averaging and prediction of sero-prevalence rate in cattle at the municipality level.

Cattle trade data were used (*i*) to assess the risk of RVFV spread through the network and (*ii*) to assess the risk of human infection with RVFV. Farms, markets, and slaughterhouses were the nodes of a directed cattle trade network. A link between two nodes corresponded to a trade movement of animals. The direction indicated the origin and destination places, and the volume was the number of traded animals.

We assessed the risk of RVFV infection in humans, using sera collected during a nationwide survey of slaughterhouse workers performed in 2008 and 2009. The study was approved by the Malagasy National Ethical Committee. Participants were included if they gave written informed consent. Sera were tested for the presence of anti-RVFV IgM, indicating a recent infection, and the results were published (13). We defined two indexes for the risk of RVFV infection in humans: (*i*) We created an index of local RVFV transmission risk, defined by the product of local predicted sero-prevalence rate in cattle and cattle density. This index was built to capture the risk associated with the primary RVFV epidemiological cycle involving mosquitoes and domestic ruminants, in the absence of known wild hosts for RVFV in Madagascar (41, 42). Humans are not involved in this cycle. Therefore, their density was not considered in the index. (*ii*) We created an index of RVFV transmission risk related to cattle trade. It was defined as the product of cattle incoming flow (number of head), predicted sero-prevalence rate in cattle at the origin, and local human density. This latter variable was included because meat consumption is proportionally higher in urban than in rural areas (43), with higher densities of slaughterhouses, butchers, and meat markets. Consequently, the risk of RVFV infection related to cattle trade should be positively correlated with human density.

The effect of these two indexes on human sero-prevalence rate was assessed with a BBLR model. Finally, a mixed-effect binomial logistic regression model was used to study the local variations of sero-prevalence rate in humans, with the administrative district and region as the nested random effects associated with the intercept. See *SI Materials and Methods* for detailed information on data sources and statistical methods, as well as links to download the datasets used in the analyses.

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